Initial REMS Approval: 02/2009
Most Recent Modification: 02/2011

APPENDIX A: SYMBICORT REMS DOCUMENT

NDA 21-929
SYMBICORT® (budesonide/formoterol fumarate dihydrate) Inhalation Aerosol

Class of Product: Long-acting beta$_2$-adrenergic agonist (LABA)

AstraZeneca Pharmaceuticals LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Contact: The Information Center at AstraZeneca
1-800-236-9933

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

1. To inform healthcare providers and prescribers of the increased risk of asthma-related death and serious outcomes associated with long-acting beta$_2$-adrenergic agonists (LABAs) including SYMBICORT.

2. To inform healthcare providers and prescribers of the appropriate use of medicines containing long acting beta$_2$-adrenergic agonists (LABAs), such as SYMBICORT.

3. To inform patients that the use of long-acting beta$_2$-adrenergic agonist (LABA) medicines, such as formoterol fumarate, one of the active moieties in SYMBICORT, is associated with an increased risk of death from asthma-related events.

4. To inform patients of other serious risks associated with SYMBICORT.

II. REMS ELEMENTS:

a) Medication Guide or PPI

A Medication Guide will be dispensed with each SYMBICORT prescription in accordance with 21 CFR 208.24.

Please see the appended Medication Guide.

b) Communication Plan

AstraZeneca will implement a communication plan targeted to healthcare providers who are likely to prescribe SYMBICORT to support the implementation of this REMS.

The communication plan will include the following elements:

1. A Dear Healthcare Provider Letter to be distributed within 60 days of the REMS approval date. The letter will provide the following safety information to current and potential prescribers of LABAs:

    a) Increased risk of asthma-related death in patients taking LABAs.

    b) New Prescribing Guidelines.

        i. SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.

        ii. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.

        iii. SYMBICORT should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

    AstraZeneca will send the Dear Healthcare Provider Letter by targeted distribution to

    - Family Practitioners
    - General Practitioners
    - Pediatricians
    - Pulmonologists
    - Internists
    - Allergists
    - Nurse Practitioners
    - Physicians Assistants

    This distribution will occur via mail or electronically. If electronic means are unsuccessful, a hardcopy will be sent. In addition to the targeted distribution, AstraZeneca also will make the Dear Healthcare Provider Letter available on the professional (HCP) website for SYMBICORT.

    Please see the appended Dear Healthcare Provider Letter.

2. Printed or web-based materials to inform healthcare providers about the occurrence of the increased risk of asthma-related deaths in patients taking LABAs and the new prescribing guidelines.

   Within 30 days of REMS approval, AstraZeneca will develop a link on the existing SYMBICORT US website for Healthcare Providers.

   The content of the web-based material will, at a minimum, include the following:

   i. Information about the risk
   ii. Key data regarding the risk
   iii. New prescribing guidelines
   iv. Currently available LABAs and approved uses
   v. Prescribing information for SYMBICORT
   vi. Patient Counseling Information
   vii. Medication Guide for SYMBICORT
   viii. Questions and Answers
   ix. Dear Healthcare Provider Letter (for a period of 1 year)
   x. External links to FDA Alert(s) for the LABAs

   This information will remain on the website for a period of 3 years.

   This new REMS content will be available to all healthcare providers as it is available on the SYMBICORT US website for Healthcare Providers.

   Please see appended web-based materials.

3. Professional Society Letter

   A Professional Society Letter will be distributed within 60 days of the REMS approval date. AstraZeneca will communicate via letter to the leadership of the following professional organizations:

   - The American Academy of Asthma Allergy & Immunology (AAAAI)
   - The American College of Allergy, Asthma & Immunology (ACAAI)
   - The American College of Chest Physicians (ACCP)
   - The American Thoracic Society (ATS)
   - The American Academy of Pediatrics (AAP),
   - The American Academy of Family Physicians (AAFP),
   - The American College of Physicians (ACP)
   - The National Medical Association (NMA)
   - The American Academy of Nurse Practitioners (AANP)
   - The American Academy of Physician Assistants (AAPA)

This communication to the societies will include the same information as that contained in the Dear Healthcare Provider Letter. AstraZeneca will request that these societies disseminate this information to their members.

Please see the appended Professional Society Letter.

c) Elements to Assure Safe Use

The REMS for SYMBICORT does not include elements to assure safe use.

d) Implementation System

Because the REMS for SYMBICORT does not include elements to assure safe use, an implementation system is not required.

e) Timetable for Submission of Assessments

AstraZeneca will submit REMS assessments to FDA annually from the date of the approval of the revised REMS. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. AstraZeneca will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B: SYMBICORT DHCPL

IMPORTANT PRESCRIBING INFORMATION

[AstraZeneca Letterhead]

[Month Year]

Dear Healthcare Professional:

AstraZeneca Pharmaceuticals LP (AstraZeneca) would like to inform you of important safety information and Prescribing Information (PI) for SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol.

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist (LABA), indicated for the treatment of asthma in patients 12 years of age and older and the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Important Safety Information related to SYMBICORT includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New Prescribing Guidelines.
    - SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
    - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
    - SYMBICORT should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

SYMBICORT has a risk evaluation and mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The SYMBICORT prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma

control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Please note that SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing SYMBICORT, please also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting $beta_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

Please instruct the patients to contact you if breathing problems worsen over time while using SYMBICORT and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the updated full Prescribing Information for SYMBICORT. In addition, please review the Medication Guide with each patient who is prescribed SYMBICORT. The Medication Guide will continue to be enclosed in each unit package.

To report adverse events among patients taking SYMBICORT, please call the AstraZeneca Information Center at 1-800-236-9933, Monday through Friday, 8 a.m. – 7 p.m. (ET), excluding holidays.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

We urge you to contact the AstraZeneca Information Center if you have any questions regarding SYMBICORT or the information contained in this letter.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President
US Strategic Development
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Enclosure

Top Navigation

Brand Logo

Prescribing SYMBICORT

- Lorem ipsum set elusmod tempor dolor inca non gataban
- Know the Risk for Asthma Patients
- Lorem ipsum
- Prescribing Information

Lorem Ipsum

Left Navigation

Know the Risk for Asthma Patients

To view each portion of the content, click the title or "+" button

- Information About the Risk
- Key Data Regarding the Risk
- New Prescribing Guidelines
- Currently Available LABAs and Approved Uses
- Patient Counseling Information
- Questions and Answers
- Dear Health Care Professional Letter
- External Links to FDA Alert(s) for the LABAs
- Prescribing Information
- Medication Guide

ISI and Approved Uses

APPENDIX D: SYMBICORT WEB-BASED MATERIALS

Printed / Web-based information:

The following content will be housed in a health care provider section of the product website.

- Information about the risk

Due to an increased risk of asthma-related death, FDA has mandated that all long-acting beta$_2$-adrenergic agonists (LABAs) and LABA-containing products, like SYMBICORT, carry a boxed warning. The boxed warning for SYMBICORT reads as follows:

WARNING: ASTHMA-RELATED DEATH
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [*see Warnings and Precautions (5.1)*].

See the full Prescribing Information for a more complete description of the risks associated with the use of SYMBICORT in the treatment of asthma.

- Key data regarding the risk

FDA's decision to require a Risk Evaluation and Mitigation Strategy (REMS) and class-labeling changes to the drug labels for long-acting beta$_2$-adrenergic agonists (LABAs) is based on analyses from the Salmeterol Multi-center Asthma Research Trial (SMART), the Salmeterol Nationwide Surveillance study (SNS), and a meta-analysis conducted by FDA in 2008 and discussed at the joint Pulmonary Allergy Drugs, Drug Safety and Risk Management, and Pediatric Advisory Committees, held on December 10-11, 2008 (for complete safety reviews and background information discussed at this meeting, see the following link: December 10-11 2008 AC meeting).

Link:
http://www.fda.gov/ohrms/dockets/ac/cder08.html#PulmonaryAllergy

SMART was a large, randomized, 28-week, placebo-controlled trial that evaluated patients 12 years of age and older receiving standard asthma therapy and the addition of either salmeterol or placebo. A total of 26,355 patients were evaluated in this study. Results showed that patients receiving salmeterol were at an increased risk for asthma-related death compared to patients receiving placebo (13/13,176 patients treated with salmeterol vs. 3/13,179 patients treated with placebo; RR 4.37, 95% CI 1.25, 15.34). Subgroup analyses were also performed and found that asthma-related death in Caucasians and African Americans occurred at a higher rate in patients using salmeterol compared to placebo. See Table 1 below for results from SMART.

Table 1. SMART Results

SMART Patients	**Asthma-Related Deaths in Salmeterol Group n (%*)**	**Asthma-Related Deaths in Placebo Group n (%*)**	**Relative Risk of Asthma-Related Death (95% Confidence Interval)**	**Excess Deaths Expressed per 10,000 Patients† (95% Confidence Interval)**
All Patients§ salmeterol: n = 13,176 placebo: n = 13,179	13 (0.10%)	3 (0.02%)	4.37 (1.25, 15.34)	8 (3, 13)
Caucasian Patients salmeterol: n = 9,281 placebo: n = 9,361	6 (0.07%)	1 (0.01%)	5.82 (0.70, 48.37)	6 (1, 10)
African American Patients salmeterol: n = 2,366 placebo: n = 2,319	7 (0.31%)	1 (0.04%)	7.26 (0.89, 58.94)	27 (8, 46)

* *28-week estimate, adjusted according to actual lengths of exposure to study treatment to account for early withdrawal of patients from the study.*

† *Estimate of the number of additional asthma-related deaths in patients treated with salmeterol in SMART, assuming 10,000 patients received salmeterol for a 28-week treatment period. Estimate calculated as the difference between the salmeterol and placebo groups in the rates of asthma-related death multiplied by 10,000.*

[§] *The Total Population includes Caucasian, African American, Hispanic, Asian, and "Other" and "not reported". No asthma-related deaths occurred in the Hispanic (salmeterol n = 996, placebo n = 999), Asian (salmeterol n = 173, placebo n = 149), or "Other" (salmeterol n = 230, placebo n = 224) subpopulations. One asthma-related death occurred in the placebo group in the subpopulation whose ethnic origin was "not reported" (salmeterol n = 130, placebo n = 127).*

The SNS was a 16-week, double-blind study that compared the addition of salmeterol or albuterol to standard asthma therapy in 25,180 asthma patients who were 12 years of age and older. In the study, there was an increase in the number of respiratory and asthma-related deaths in the salmeterol group (0.07% [12 out of 16,787 patients]) compared to the albuterol group (0.02% [2 out of 8,393 patients] relative risk of 3.0, p=0.105).

In preparation for the December 2008 Advisory Committee, FDA conducted a meta-analysis of 110 studies evaluating the use of LABAs in 60,954 patients with asthma. The meta-analysis used a composite endpoint to measure severe exacerbation of asthma symptoms (asthma-related death, intubation, and hospitalization). The results of the meta-analysis suggested an increased risk for severe exacerbation of asthma symptoms in patients using LABAs compared to those not using LABAs. The largest risk difference per 1000 treated patients was seen in children 4-11 years of age; see Table 2 below. The results of the meta-analysis were primarily driven by asthma-related hospitalizations. Other meta-analyses evaluating the safety of LABAs in the treatment of asthma have not shown a significant increase in the risk for severe asthma exacerbations.

Table 2. Meta-Analysis Results: Number of Patients Experiencing an Event[¶]

Patient Population	**LABA Patients Experiencing an Event**	**Non-LABA Patients Experiencing an Event**	**Risk Difference Estimate Per 1000 Treated Patients**	**95% Confidence Interval**
All Patients n = 30,148 LABA patients n = 30,806 non-LABA patients	381	304	2.80	1.11 – 4.49
Patients ages 12 to 17 years n = 3,103 LABA patients n = 3,289 non-LABA patients	48	30	5.57	0.21 – 10.92

Patients ages 4 to 11 years n = 1,626 LABA patients n = 1,789 non-LABA patients	61	39	14.83	3.24 - 26.43

¶ *Event defined as the composite end point (asthma-related death, intubation, and hospitalization)*

At this time, there are insufficient data to conclude whether using LABAs with an inhaled corticosteroid reduces or eliminates the risk of asthma-related death and hospitalizations. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used in conjunction with an inhaled corticosteroid.

Based on the available information, FDA concludes there is an increased risk for severe exacerbation of asthma symptoms, leading to hospitalizations in pediatric and adult patients as well as death in some patients using LABAs for the treatment of asthma. The Agency is requiring the implementation of a REMS and class-labeling changes to improve the safe use of these products.

See February 2010 LABA Drug Safety Communication for more information.

Link:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm

- New prescribing guidelines

Long-acting beta$_2$-agonists (LABAs), a class of medications used for the treatment of asthma, now have new recommendations in their drug label intended to promote their safe use in the treatment of asthma.

In February 2010, the Agency announced it was requiring manufacturers to revise their drug labels because of an increased risk of severe exacerbation of asthma symptoms, leading to hospitalizations, in pediatric and adult patients, as well as death in some patients using LABAs for the treatment of asthma (see February 2010 LABA Drug Safety Communication).

In June 2010, the agency issued updated recommendations on the appropriate use of LABAs. See June 2010 LABA Drug Safety Communication for more information.

Link:
http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProvider

s/ucm213836.htm

The new recommendations in the updated labels state:

- Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

FDA has stated its belief that when LABAs are used according to the recommendations outlined above and in the approved drug labels, the benefits of LABAs in improving asthma symptoms outweigh their risks of increasing severe asthma exacerbations and deaths from asthma.

- Currently available LABAs and approved uses

FDA Approved Long-Acting Beta Agonists

Brand Name[#]	**LABA Active Ingredient**	**Corticosteroid Active Ingredient**	**FDA-Approved Uses**[**]
SYMBICORT® Inhalation Aerosol	Formoterol	Budesonide	Asthma, COPD
Dulera® Inhalation Aerosol	Formoterol	Mometasone	Asthma
Serevent® Diskus®	Salmeterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil® Aerolizer®	Formoterol	None	Asthma, COPD, exercise-induced bronchospasm
Foradil® Certihaler®††	Formoterol	None	Asthma
Advair Diskus®	Salmeterol	Fluticasone	Asthma, COPD
Advair® HFA	Salmeterol	Fluticasone	Asthma
Brovana®	Arformoterol	None	COPD
Perforomist®	Formoterol	None	COPD

[#] All trademarks are the property of their respective owners.

[**] Please see prescribing information for respective products for complete product information.

†† Not currently marketed in the US.

- Prescribing information for SYMBICORT

Link to Prescribing information for SYMBICORT

- Patient Counseling Information

Patient Counseling Information

See US Prescribing Information and Medication Guide

Asthma-Related Death
See Medication Guide
Patients should be informed that formoterol fumarate dihydrate, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of SYMBICORT, or other long-term asthma-control drugs mitigate this risk. See WARNINGS AND PRECAUTIONS Section 5.1 of the full Prescribing Information.

Not for Acute Symptoms
SYMBICORT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:
- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.

Do Not Use Additional Long-Acting Beta$_2$-Agonists
When patients are prescribed SYMBICORT, other long-acting beta$_2$-agonists should not be used. See WARNINGS AND PRECAUTIONS Section 5.3 of the full Prescribing Information.

Risks Associated With Corticosteroid Therapy
Local Effects: Patients should be advised that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with SYMBICORT, but at times therapy with SYMBICORT may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See WARNINGS AND PRECAUTIONS Section 5.4 of the full Prescribing

Information.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia. See WARNINGS AND PRECAUTIONS Section 5.5 of the full Prescribing Information.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See WARNINGS AND PRECAUTIONS Section 5.6 of the full Prescribing Information.

Hypercorticism and Adrenal Suppression: Patients should be advised that SYMBICORT may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to SYMBICORT. See WARNINGS AND PRECAUTIONS Section 5.8 of the full Prescribing Information.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased Bone Mineral Density (BMD) should be advised that the use of corticosteroids may pose an additional risk. See WARNINGS AND PRECAUTIONS Section 5.13 of the full Prescribing Information.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route. See WARNINGS AND PRECAUTIONS Section 5.14 of the full Prescribing Information.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered. See WARNINGS AND PRECAUTIONS Section 5.15 of the full Prescribing Information.

Risks Associated With Beta-Agonist Therapy
Patients should be informed of adverse events associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor or nervousness. See WARNINGS AND PRECAUTIONS Section 5.12 of the full Prescribing Information.

- Medication Guide for SYMBICORT

Link to Medication Guide for SYMBICORT

- Questions and Answers

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

Q2. What is the goal of the new risk management program for LABAs?

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

Q4. What are the names of LABA-containing medicines used to treat asthma?

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

Q6. What information did FDA review to help the Agency decide to require a risk management program?

Q7. Why is the new risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

Questions about SYMBICORT Inhalation Aerosol

Q1. Why does SYMBICORT have a boxed warning?

Q2. What should I tell patients about the risk of asthma-related death?

Q3. Can SYMBICORT be used for acute asthma symptoms?

Q4. Can additional LABAs be used with SYMBICORT?

Q5. What are the risks of corticosteroid therapy?

Q6. What are the risks of beta-agonist Therapy?

Questions about LABA Safety and Risk Evaluation and Mitigation Strategy (REMS) for LABAs

Q1. Why is FDA requiring LABA manufacturers to have a risk management program for these medicines?

A. Despite the benefits of long-acting beta$_2$-agonists (LABAs) in helping people with asthma and COPD breathe easier, FDA's analyses indicate there is an increase in the risk of severe exacerbation of asthma symptoms in some patients with asthma that use a LABA compared to patients with asthma that do not use a LABA. Because of this risk, FDA wants to make sure LABAs are used appropriately in patients with asthma. Even though LABAs are approved for use in asthma and COPD, FDA's new recommendations only apply to the use of LABAs in the

treatment of asthma. In order to ensure the safe use of these medicines, FDA is requiring the manufacturers of LABAs to develop this risk management program for healthcare professionals and patients.

Q2. What is the goal of the new risk management program for LABAs?

A. The risk management program for LABAs requires the manufacturers to better inform healthcare professionals and patients about the risk of LABAs for patients with asthma and ways to decrease that risk while maintaining the benefits of the drug. Under the program, patients who have a prescription filled for a LABA will receive a revised Medication Guide that explains the risks and benefits of the medicine. In addition manufacturers of LABAs will update the prescribing information they provide to healthcare professionals to include the latest recommendations for safe use of these important medicines.

Q3. What are the key points people should know about the safe use of LABAs in patients with asthma?

A. The key points are:

- Single-ingredient LABAs should only be used in combination with an asthma controller medication; they should not be used alone.
- LABAs should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.
- LABAs should only be used as additional therapy for patients with asthma who are currently taking but are not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid.
- Once asthma control is achieved and maintained, patients should be assessed at regular intervals and step down therapy should begin (e.g., discontinue LABA), if possible without loss of asthma control, and the patient should continue to be treated with a long-term asthma control medication, such as an inhaled corticosteroid.

Q4. What are the names of LABA-containing medicines used to treat asthma?

A. Below are the names of the LABA-containing medicines approved by FDA to treat asthma:

Brand Name(s)	Generic Name(s)	Description
SYMBICORT Inhalation Aerosol	formoterol and budesonide	formoterol is a LABA and budesonide is a corticosteroid long-term asthma control medication
Dulera Inhalation Aerosol	formoterol and mometasone	formoterol is a LABA and mometasone is a corticosteroid long-term asthma control medication
Advair Diskus, Advair HFA	salmeterol and fluticasone	salmeterol is a LABA and fluticasone is a corticosteroid long-term asthma control

		medication
Serevent Diskus	salmeterol	single ingredient LABA with no corticosteroid long-term asthma control medication
Foradil Aerolizer	formoterol	single ingredient LABA with no corticosteroid long-term asthma control medication

Q5. Why should LABAs only be used with a long-term asthma control medication, are they safer when used this way?

A. At this time, there is no conclusive evidence that the combination of a long-term asthma control medication with a LABA decreases or eliminates the risk of a LABA. More study and analysis is required in this area. FDA is requiring the manufacturers of LABAs to conduct studies evaluating the safety of LABAs when used with an inhaled corticosteroid to better understand this issue.

Because of the risks of LABAs, FDA recommends that a LABA should not be used for a patient whose asthma can be controlled with long-term asthma control medication, such as an inhaled corticosteroid. If a LABA needs to be added to that medicine, it should only be used until the patient's healthcare professional determines their asthma is under control, and then the LABA should be stopped if possible. This means it is always necessary for a patient to use a LABA in combination with a long-term asthma control medication.

Q6. What information did FDA review to help the Agency decide to require a risk management program?

A. FDA used a variety of studies and research in patients with asthma using a LABA. Two specific studies that provided valuable information were 1) the Salmeterol Multicenter Asthma Research Trial (SMART) and 2), the Salmeterol Nationwide Surveillance study (SNS). Salmeterol is the LABA in Serevent. Each of these studies showed a higher risk of death for patients with asthma that used a LABA (salmeterol) compared to patients with asthma that did not use a LABA. In addition, FDA used a research method called a meta-analysis to further understand the risks associated with the use of LABAs in patients with asthma. A meta-analysis uses data from multiple studies on a particular topic to enable scientists to combine information from those studies to make scientific conclusions or recommendations in that area. For more information on these specific studies, please see February 2010 LABA Drug Safety Communication for more information.

Q7. Why is the new risk management program designed for patients with asthma and not for patients with COPD, aren't LABAs used to treat both conditions?

A. LABAs are used to treat both asthma and COPD; however, the studies reviewed by FDA included patients using LABAs for the treatment of asthma. These studies indicated an increased risk of severe exacerbation of asthma symptoms leading to hospitalization and death in these patients. There is no evidence to conclude that people with COPD who use LABAs are at any

greater risk compared to people with COPD who do not use LABAs. FDA does not recommend any change in the use of LABAs for COPD.

Questions about SYMBICORT Inhalation Aerosol

Q1. Why does SYMBICORT have a boxed warning?

A. Due to an increased risk of asthma-related death, FDA has mandated that all long-acting beta$_2$- agonists (LABAs) and LABA-containing products, like SYMBICORT, carry a boxed warning. The boxed warning for SYMBICORT reads as follows:

WARNING: ASTHMA-RELATED DEATH
Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids [*see Warnings and Precautions (5.1)*].

See the full Prescribing Information for a more complete description of the risks associated with the use of SYMBICORT in the treatment of asthma.

Q2. What should I tell patients about the risk of asthma-related death?

A. Patients should be informed that formoterol fumarate dihydrate, one of the active ingredients in SYMBICORT, increases the risk of asthma-related death and may increase the risk of asthma-related hospitalization in pediatric and adolescent patients. They should also be informed that data are not adequate to determine whether the concurrent use of inhaled corticosteroids, the other component of SYMBICORT, or other long-term asthma-control drugs mitigate this risk. See WARNINGS AND PRECAUTIONS Section 5.1 of the full Prescribing Information.

Q3. Can SYMBICORT be used for acute asthma symptoms?

A. No. SYMBICORT is not meant to relieve acute asthma symptoms or exacerbations of COPD and extra doses should not be used for that purpose. Acute symptoms should be treated with an inhaled, short-acting beta$_2$-agonist such as albuterol. (The physician should provide the patient with such medication and instruct the patient in how it should be used.)

Patients should be instructed to notify their physician immediately if they experience any of the following:

- Decreasing effectiveness of inhaled, short-acting beta$_2$-agonists
- Need for more inhalations than usual of inhaled, short-acting beta$_2$-agonists
- Significant decrease in lung function as outlined by the physician

Patients should not stop therapy with SYMBICORT without physician/provider guidance since symptoms may recur after discontinuation.

Q4. Can additional LABAs be used with SYMBICORT?

A. No. When patients are prescribed SYMBICORT, other long-acting beta$_2$-agonists should not be used. See WARNINGS AND PRECAUTIONS Section 5.3 of the full Prescribing Information.

Q5. What are the risks of corticosteroid Therapy?

A. Local Effects: Patients should be advised that localized infections with Candida albicans occurred in the mouth and pharynx in some patients. If oropharyngeal candidiasis develops, it should be treated with appropriate local or systemic (i.e., oral) antifungal therapy while still continuing therapy with SYMBICORT, but at times therapy with SYMBICORT may need to be temporarily interrupted under close medical supervision. Rinsing the mouth after inhalation is advised. See WARNINGS AND PRECAUTIONS Section 5.4 of the full Prescribing Information.

Pneumonia: Patients with COPD have a higher risk of pneumonia and should be instructed to contact their healthcare provider if they develop symptoms of pneumonia. See WARNINGS AND PRECAUTIONS Section 5.5 of the full Prescribing Information.

Immunosuppression: Patients who are on immunosuppressant doses of corticosteroids should be warned to avoid exposure to chicken pox or measles and, if exposed, to consult their physician without delay. Patients should be informed of potential worsening of existing tuberculosis, fungal, bacterial, viral, or parasitic infections, or ocular herpes simplex. See WARNINGS AND PRECAUTIONS Section 5.6 of the full Prescribing Information.

Hypercorticism and Adrenal Suppression: Patients should be advised that SYMBICORT may cause systemic corticosteroid effects of hypercorticism and adrenal suppression. Additionally, patients should be instructed that deaths due to adrenal insufficiency have occurred during and after transfer from systemic corticosteroids. Patients should taper slowly from systemic corticosteroids if transferring to SYMBICORT. See WARNINGS AND PRECAUTIONS Section 5.8 of the full Prescribing Information.

Reduction in Bone Mineral Density: Patients who are at an increased risk for decreased Bone Mineral Density (BMD) should be advised that the use of corticosteroids may pose an additional risk. See WARNINGS AND PRECAUTIONS Section 5.13 of the full Prescribing Information.

Reduced Growth Velocity: Patients should be informed that orally inhaled corticosteroids, a component of SYMBICORT, may cause a reduction in growth velocity when administered to pediatric patients. Physicians should closely follow the growth of children and adolescents taking corticosteroids by any route. See WARNINGS AND PRECAUTIONS Section 5.14 of the full Prescribing Information.

Ocular Effects: Long-term use of inhaled corticosteroids may increase the risk of some eye problems (cataracts or glaucoma); regular eye examinations should be considered. See WARNINGS AND PRECAUTIONS Section 5.15 of the full Prescribing Information.

Q6. What are the risks of beta-agonist Therapy?

A. Patients should be informed of adverse events associated with $beta_2$-agonists, such as palpitations, chest pain, rapid heart rate, tremor or nervousness. See WARNINGS AND PRECAUTIONS Section 5.12 of the full Prescribing Information.

- Dear Healthcare Provider Letter (for a period of 1 year)

Link to Dear Healthcare Provider Letter

- External links to FDA Alert(s) for LABAs

For more information:

LINK: http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm199565.htm

APPENDIX C: SYMBICORT DEAR MEDICAL SOCIETY LETTER

IMPORTANT PRESCRIBING INFORMATION

[AstraZeneca Letterhead]

[Month Year]

Dear (Medical Society):

AstraZeneca Pharmaceuticals LP (AstraZeneca) would like to inform you of important safety information and Prescribing Information (PI) for SYMBICORT® (budesonide and formoterol fumarate dihydrate) Inhalation Aerosol.

SYMBICORT is a combination product containing a corticosteroid and a long-acting beta$_2$-adrenergic agonist (LABA), indicated for the treatment of asthma in patients 12 years of age and older and the maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) including chronic bronchitis and emphysema. SYMBICORT is NOT indicated for the relief of acute bronchospasm.

Important Safety Information related to SYMBICORT includes:

- Increased risk of asthma-related death in patients taking LABAs.
- New Prescribing Guidelines.
    - SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA.
    - Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid.
    - SYMBICORT should not be used in patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

SYMBICORT has a risk evaluation and mitigation strategy (REMS) that consists of a Medication Guide and a communication program.

The SYMBICORT prescribing information includes a boxed warning to highlight the safety issue of asthma-related death.

WARNING: ASTHMA-RELATED DEATH

Long-acting beta$_2$-adrenergic agonists (LABA), such as formoterol one of the active ingredients in SYMBICORT, increase the risk of asthma-related death. Data from a large placebo-controlled U.S. study that compared the safety of another long-acting beta$_2$-adrenergic agonist (salmeterol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patients receiving salmeterol. This finding with salmeterol is considered a class effect of the LABA, including formoterol. Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, SYMBICORT should only be used for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and LABA. Once asthma

control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue SYMBICORT) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use SYMBICORT for patients whose asthma is adequately controlled on low or medium dose inhaled corticosteroids.

Please note that SYMBICORT should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma.

When prescribing SYMBICORT, the healthcare professional should be guided to also provide the patient with an inhaled, short-acting $beta_2$-agonist (e.g., albuterol) to be used as a rescue inhaler for treatment of acute symptoms. Increasing use of inhaled, short-acting $beta_2$-agonists is a marker for deteriorating asthma. In this situation, the patient requires immediate re-evaluation with reassessment of the treatment regimen.

The healthcare professional should instruct the patients to contact them if breathing problems worsen over time while using SYMBICORT and get emergency medical care if breathing problems worsen quickly and are not being relieved by the use of the rescue inhaler.

Please take time to read the updated full Prescribing Information for SYMBICORT.

Please share this communication with the members of your society and assure that they review the Medication Guide with each patient who is prescribed SYMBICORT. The Medication Guide will continue to be enclosed in each unit package.

To report adverse events among patients taking SYMBICORT, please call the AstraZeneca Information Center at 1-800-236-9933, Monday through Friday, 8 a.m. – 7 p.m. (ET), excluding holidays.

Alternatively, adverse event information may be reported to FDA's MedWatch Reporting System by:

- Phone at 1-800-FDA-1088 (1-800-332-1088)
- Facsimile at 1-800-FDA-0178 (1-800-332-0178)
- Mail using FDA Form 3500 located at http://www.fda.gov/medwatch

We urge you to contact the AstraZeneca Information Center if you have any questions regarding SYMBICORT or the information contained in this letter.

Sincerely,

James W. Blasetto, M.D., MPH
Vice President
US Strategic Development
AstraZeneca LP
1800 Concord Pike
P.O. Box 8355
Wilmington, DE 19803-8355

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SALLY M SEYMOUR
02/16/2011